polysaccharide or the de-N-acetylated oligosaccharide is at least 95% N-acryloylated.

61. (Amended) The conjugate according to claim 1, wherein the N-propionated polysaccharide or N-propionated oligosaccharide at least 50% de-N-acetylated.

62. (Amended) The conjugate according to claim 16, wherein the de-N-acetylated polysaccharide or the de-N-acetylated oligosaccharide is at least 50% de-N-acetylated.

63. (Amended) The conjugate according to any one of claim 1 and claim 16, wherein the bacterial protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, cholera toxin subunit B, *Neisseria meningitidis* outer membrane proteins, pneumolysoid, C-β protein from group B Streptococcus, *Pseudomonas aeruginosa* toxoid, and pertussis toxoid.

IN THE SPECIFICATION

Please replace the first sentence of the instant specification with the following:

This application claims priority under 35 U.S.C. §119(e) for Provisional Application Serial No. 60/097,120, filed August 19, 1998, by Michon, et al. and entitled, "Immunogenic Polysaccharide-Protein Conjugate Useful As A Vaccine Produced Via Conjugation Through A C2-3 N-Acyl Portion Of A Polysaccharide."

REMARKS

No new matter is introduced by the amendments.

Claims 1-63 are pending. Please cancel claim 2 without prejudice. Please cancel claims 6, 7, 29-37, and 41-58 without prejudice as they have been withdrawn from consideration. Claims 1-5, 8-28, 38-40, and 59-63 stand rejected.

Claim 1 has been amended in order to more clearly state that an aspect of the claimed conjugates is the ability to elicit protective antibodies reactive against the N-propionated polysaccharide or N-propionated oligosaccharide (pg. 23, lns. 1-6 and pg. 14, lns. 23-27). The claimed conjugate further claims at least 50% of the N-propionated polysaccharide or oligosaccharide is de-N-acetylated which is supported by the instant specification at page 6, ln. 13.

OBJECTIONS

15) The Examiner maintains the objection to the specification made in paragraph 7(a) of the Office Action mailed 1/28/02 (paper no. 11) for the first paragraph of the

specification because a clean and a marked-up version of the first paragraph of the specification was not submitted. Applicants respectfully submit herewith, a clean and a marked-up version of the first paragraph of the specification. Reconsideration and withdrawal of this objection is respectfully requested.

16) The objection to the specification made in paragraph 7(c) of the Office Action mailed 1/28/02 has been maintained because the Examiner contends the recitations "N-propionated polysaccharide" and "N-propionated oligosaccharide" in claim 16 do not have antecedence in the specification. Applicants respectfully disagree with the Examiner's objection.

The Examiner has objected to the specification as failing to provide proper antecedent basis for the claimed subject matter. However, the specification does provide proper antecedent basis for the subject matter as claimed in claim 16, specifically the recitation "N-propionated" polysaccharide or oligosaccharide. The Examiner's attention is respectfully directed to the MPEP 2173.05(e) under "A claim term which has no antecedent basis in the disclosure is not necessarily indefinite." The MPEP states on page 2100-200:

> The mere fact that a term or phrase used in the claim has no antecedent basis in the specification disclosure does not mean, necessarily, that the term or phrase is indefinite. There is no requirement that the words in the claim must match those used in the specification disclosure. (emphasis added)

Since the MPEP states that the exact term or phrase used in the claim is not required in the specification, the instant specification need only define "N-propionated" polysaccharide or oligosaccharide in a manner that one skilled in the art would understand. "N-propionated" polysaccharide or oligosaccharide are described on page 10, lines 6-14, where "The N-acryloylated polysaccharide is then directly coupled to protein under optimum conditions of pH, temperature and time to form an immunogenic β-propionamido-linked polysaccharide-protein conjugate." Also, the instant specification describes using a polysaccharide or oligosaccharide for preparing the β-propionamido-linked polysaccharide- and β-propionamido-linked oligosaccharide- protein conjugates of the present invention (pg. 11, lns. 13-24). The N-acryloylating de-acetylated polysaccharide or oligosaccharide step that forms an N-propionated polysaccharide or oligosaccharide is described in the instant

specification and shown in the schematic drawing (see Figure 1) in such a manner that one skilled in the art would understand "N-propionated" polysaccharide or oligosaccharide to be those polysaccharides or oligosaccharides linked by a β-propionamido bond to an acryloylating reagent. Thus, the specification supports claim 16 because it discloses "N-propionated polysaccharide" or "N-propionated oligosaccharide" in such a manner that the skilled artisan would be knowledgeable as to its meaning. "N-propionated" polysaccharide or oligosaccharide is clearly understood and supported by the specification, applicants respectfully request reconsideration and withdrawal of this objection.

REJECTIONS UNDER 35 U.S.C. §112

33) Claims 18 and 20 stand rejected under 35 U.S.C. §112, first paragraph as being non-enabled with regard to the scope. Specifically, the Examiner uses Romanowska, et al.; Roy, et al. (1990); Roy, et al. (1991); and Pon for support showing that conjugation by Michael addition is carried out in an alkaline pH. Applicants respectfully traverse this ground of rejection.

The protein conjugates of claims 18 and 20 are enabled and supported by the disclosure of the instant application since the specification contains sufficient information regarding the protein conjugates of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. The Examiner contends that the "art indicates that conjugation by Michael addition is carried out in the alkaline range, i.e., above 9.0 in an appropriate buffer, such as, borate or carbonate buffer" (Paper No. 17; pg. 7, lns 4-5). Furthermore, the Examiner contends that in order to practice the invention as claimed, undue experimentation would have been required "due to the lack of guidance/evidence, lack of working examples, the uncertainty with regard to conjugation by Michael addition taking place at a non-alkaline pH of 7.0 and in a phosphate buffer medium and the quantity of experimentation necessary" (Paper No. 17; pg. 7, lns 17-20). However, applicants respectfully disagree.

The Examiner's attention is respectfully directed to page 10, ln. 15 through page 11, ln. 3 of the instant specification which specifically addresses one embodiment of the invention directed to conjugation of a protein, which has more reactive cysteine residues than reactive lysine residues, at a neutral pH. Working examples describing this particular embodiment are found in Example 1. In particular, the sections entitled "Preparation of

Thiolated rPorB," and "Preparation of N-Acryloylated K1-S-rPorB Conjugate (K1-S-PorB)" describe conjugating a protein through the thiol group of a cysteine residue to a polysaccharide. Figure 1 shows a scheme of the coupling reaction, where conjugation through the amino group of lysine occurs at a basic pH and conjugation, and where coupling through the thiol group of cysteine occurs at a neutral pH. The instant specification, including Figure 1 and Example 1, provides guidance for selecting an appropriate pH at which to conduct the conjugation based on the number of reactive groups. According to the instant specification, if the protein has more reactive lysine residues as compared to reactive cysteine residues, then the conjugation method is performed at a basic pH (pg. 10, lns. 21-23). If the protein has more reactive cysteine residues as compared to reactive lysine residues, then the conjugation method is performed at a neutral pH (pg. 10, lns. 23-25). In fact, "conjugation is conducted at a neutral pH of about 7.0 for optimal reactivity of thiol (SH) groups of cysteine residues of the protein" (pg. 10, lns. 17-19). One skilled in the art would understand how to make the thiolated rPorB prepared in "0.25 M HEPES buffer of pH 7 containing 0.25 M sodium chloride and 0.05% zwittergent 3-14" (pg. 20, lns. 29-30) conjugated to the N-acryloylated K1 polysaccharide as described on page 21 of the instant specification. Support for claim 20, where conjugates are coupled in a reagent including phosphate buffer, bicarbonate buffer, and borate buffer, may be found in the instant specification on page 10, lns. 26-28. Example 1 demonstrates that these buffers may be used appropriately in coupling reactions at basic pH (pg. 18, Section D. "Coupling of the type 14 N-acryloylated pneumococcal polysaccharide to tetanus toxoid monomer" through pg. 20, Section H. "β-propionamido-linked K1-rPorB conjugate (K1-rPorB I)").

Furthermore, one skilled in the art would understand how to use the conjugate of the present invention. Applicants respectfully direct the Examiner's attention to the instant specification which reports of the immunogenicity of the protein conjugates of the instant invention (Example 2: pgs. 26-27; Tables 7-8) as determined by *in vivo* mouse studies. The tables indicate that the protein conjugates of the invention, coupled through the amino or thiol group, are in fact immunogenic. Therefore, the present invention enables and provides sufficient guidance for one skilled in the art to construct and use the N-propionated saccharide-protein conjugates.

Romanowska, et al. merely report that direct coupling of lysyl ε-amino groups

of protein, in basic conditions was efficient for Michael additions (pg. 101). However, the Romanowska reference does not support coupling a protein composed of more reactive cysteine residues than reactive lysine residues. Applicants' "method of conjugation using a protein composed of more reactive cysteine residues as compared to lysine residues is preferably conducted at about a neutral pH" (pg. 10, lns. 23-25). Therefore, Romanowska, et al. does not teach away from the embodiment of the present invention which claims coupling a protein which has more reactive cysteine residues than reactive lysines residues at about a neutral pH.

Roy, et al. (1990) reports a Michael addition using basic pH for coupling sialyloligosaccharide-protein conjugates. Once again, this reference does not mention coupling a protein having more reactive cysteine residues than reactive lysine residues. Roy, et al. (1991) also reports coupling by Michael addition using a carbonate buffer at pH 9 through the amino group of a protein (Scheme 1). Neither of these references teach away from the neutral pH embodiment of the present invention which couples through the thiol group of a protein composed of more reactive cysteine residues than reactive lysine residues.

The Pon publication reports polysialic acid conjugates where Michael addition at a basic pH is used for coupling. The coupling occurs through the amino group of the protein. Pon does not report of conjugating through the thiol group of a cysteine residue of the protein.

Therefore, none of the publications relied on by the Examiner are appropriate. These publications merely report synthesis of protein conjugates where coupling occurs at a basic pH through the amino group of the protein. Since applicants' claims 18 and 20 refer to coupling polysaccharides and proteins at a neutral pH and using specific reagents for coupling, respectively, the cited publications are improperly relied on to support the Examiner's contentions that conjugation at a neutral pH is not enabled. Applicants' instant specification, Examples 1 and 2, and Figure 1 provide sufficient guidance and enablement for one skilled in the art to produce the claimed immunogenic protein conjugates. Therefore, reconsideration and withdrawal of this §112, first paragraph rejection is respectfully requested.

34) Claims 37-40 stand rejected under 35 U.S.C. §112, first paragraph as being non-enabled with regard to the scope. Applicants respectfully traverse the Examiner's

rejection.

The Examiner contends that a type III GBS capsular polysaccharide-protein conjugate would not and could not be expected to provide protective immunity against other of members of the genus Streptococcus, other than type III GBS because of the immunological or biological specificity of the polysaccharide used in the conjugate. The polysaccharide component of the polysaccharide-protein conjugates of claims 37-40 are extracted from the organism or cell of interest and used to make vaccines that provide protective immunity against the specific organism from which the polysaccharide was obtained (pg. 12, "Vaccines"). The β-propionamido-linked polysaccharide-protein conjugates of the present invention are used as antigens to generate antibodies that are reactive against the polysaccharide or oligosaccharide and thereby reactive against the organism or cell from which the polysaccharide or oligosaccharide was isolated. The vaccines comprising these conjugates, thus elicit antibodies reactive against the polysaccharide and organism or cell from which the polysaccharide was obtained. The Examiner contends that the recitation "organism" encompasses several entities including a fungus, a parasite, a bacterium, a yeast, a virus, etc. Further, the Examiner contends that the phrase "at least one member of a genus of an organism" encompasses a myriad of homologous and heterologous members of a bacterial, fungal, or parasitic genus. One skilled in the art would understand that the vaccines comprising the polysaccharide protein conjugate would be immunogenic to the organism or cell from which the polysaccharide was obtained. Accordingly, applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

38) Claims 1-5, 8-28, 37-40, and 59-63 stand rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this ground of rejection.

The Examiner contends that there is no descriptive support for the broader limitations including: "N-propionated saccharide;" "N-propionated saccharide is de-N-acetylated and N-acryloylated at the de-N-acetylated terminus;" and "directly coupled at a beta position of a propionate moiety." Applicants respectfully traverse this rejection. With

respect to the recitation "saccharide," one skilled in the art would understand the meaning where polysaccharides and oligosaccharides are several simple sugars linked together. However, in order to address the Examiner's concerns, applicants have amended claims 1-5, 8-28, 37-40, and 59-63 to substitute the term "saccharide" with either - -polysaccharide- - or - -oligosaccharide- -.

Applicants respectfully direct the Examiner's attention to the instant specification which provides support for the phrases "N-propionated saccharide is de-N-acetylated and N-acryloylated at the de-N-acetylated terminus" and "directly coupled at a beta position of a propionate moiety" (pg. 4, lns. 10-15).

> A method of preparing an immunogenic polysaccharide-protein conjugate is provided which comprises de-N-acetylation of a polysaccharide or an oligosaccharide by base or enzymatic hydrolysis followed by N-acryloylation of the N-deacetylated polysaccharide. The N-acryloylated polysaccharide is directly coupled to a carrier protein to form the immunogenic β-propionamido-linked polysaccharide-protein conjugate.

One skilled in the art would understand the de-N-acetylation and N-acryloylation steps as described in the instant specification and as detailed in Example 1, where the polysaccharide is first depolymerized, de-N-acetylated, N-acryloylated, then coupled to a protein (pgs. 17-20) and specifically regarding coupling through thiol groups (pgs. 20-21). Furthermore, the skilled artisan would be knowledgeable as to how a polysaccharide or oligosaccharide is directly coupled to a protein to form a β-propionated polysaccharide-protein conjugate from the detailed description provided in Example 1 "Preparation of ß-Propionamido-Linked Polysaccharide-Protein Carrier Conjugates." As previously discussed in paragraph 16), there is no requirement that the words in the claim must match those used in the specification disclosure. Since one skilled in the art would understand the recitations mentioned above, the instant specification is enabling and provides sufficient guidance for the skilled artisan to make and use the polysaccharide or oligosaccharide-protein conjugate as claimed. Applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

35 U.S.C. §112, SECOND PARAGRAPH

35) The Examiner rejects claims 3-5 under 35 U.S.C. §112, second paragraph as

being vague and indefinite in the recitation "derived," because it is unclear what the process of "deriving" encompasses. Applicants respectfully disagree with this rejection.

The term "derived" is defined by *The American Heritage® Dictionary of the English Language*, Fourth Edition © 2000 by Houghton Mifflin Company as "to obtain or receive from a source" and in regards to Chemistry, "to produce or obtain (a compound) from another substance by chemical reaction." Furthermore, applicants believe that the term "derived" is proper and appropriate as claimed and described in the instant specification. However, in order to address the Examiner's concerns, applicants have substituted the term "derived" with - -obtained- -. Therefore, reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

39) Claims 1-5, 8-28, 37-40, and 59-63 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite, failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully disagree with the Examiner's grounds for rejection.

(a) In particular, claims 1 and 16 stand rejected for being vague and indefinite in the recitation "directly coupled to" and "directly coupling," respectively, because the Examiner believes that the limitation is unclear. Specifically, the Examiner is unclear as to whether or not this limitation represents covalent coupling or non-covalent coupling.

Applicants respectfully disagree with the Examiner's contention that the recitation "directly coupled to" and "directly coupling" is vague and indefinite. "Directly coupled" is well understood in the art to mean two items joined or linked together. "Indirectly coupled" is understood to mean two items joined together through an intermediate linker molecule. In fact, on page 2, lns. 4-8 of the instant specification, several examples in the art report conjugation methods and "direct and indirect coupling of polysaccharides to proteins to form conjugates (summarized in Ref. (11) and U.S. Patent No. 5,306,492). Conjugation methods have included diazo coupling, thioether bond, amidation, reductive amination and thiocarbamoyl for coupling a polysaccharide to a protein carrier." One skilled in the art would understand the meaning of direct versus indirect coupling to mean a polysaccharide linked to a protein without a linker molecule and with a linker molecule, respectively. Applicants respectfully direct the Examiner's attention to William E. Dick, Jr. and Michel Beurret (Cruse JM, Lewis RE Jr (eds): Conjugate Vaccines. Contrib Microbiol

Immunol. Basel, Karger, 1989, vol. 10, pp. 48-114) where on pages 70-73, conjugate vaccines have two types of linkages, direct coupling and those "coupling with a linker (spacer) chain." One skilled in the art would understand directly coupled conjugates to mean a polysaccharide linked to a protein without a linker molecule or spacer. Therefore, direct coupling was well understood in the art at the time the instant application was filed. Additionally, the chemical structure of Figure 1 clearly shows an N-propionated saccharide linked to a protein, i.e., H_2N-Lys-Pro or HS-Cys Pro. There is no linker or spacer molecule depicted in the scheme of Figure 1, which simply shows a Michael-type addition which is commonly understood to mean a 1, 4-conjugate addition (pg. 5, lns. 17-19). Therefore, the recitation "directly coupled" is well understood in the art, as well as, described in the instant specification. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

(b) The Examiner rejects claims 4, 15, 59, 61, and 63 for allegedly lacking antecedent basis for the recitation "The conjugates according to claim 1" [Emphasis added] (Paper No. 17, page 12). In order to expedite prosecution of this application, applicants have amended the claims to replace "conjugates" with - - conjugate- -. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

(c) Claims 60 and 62 stand rejected for allegedly lacking antecedent basis for the recitation: "The conjugates according to claim 16." Applicants respectfully disagree with this ground for rejection, but have amended the claims by replacing "conjugates" with - - conjugate- - in order to address the Examiner's concerns. Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(c) The Examiner rejects claim 4 for being incorrect and/or redundant in the recitation "the the" saccharide. Applicants have deleted the second "the" in order to address the Examiner's concerns and respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

(d) Claims 59 and 61 stand rejected for lacking antecedent basis for the recitation "the saccharides are." Applicants have amended the claims by replacing "the saccharides are" with - -the saccharide is- - in order to address the Examiner's concerns. Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(e) Claim 1 stands rejected to for being unclear as to what the antibodies are protective against. The Examiner contends that the specificity of these antibodies is not

understood. In order to address the Examiner's concerns, applicants have amended claim 1 to read - -elicits protective antibodies reactive against the N-propionated polysaccharide or N-propionated oligosaccharide- -. Support is provided in the instant specification under sections "C. Vaccines" (pg. 12, lns. 1-6) and "E. Antibodies" (pg. 14, lns. 23-27). The "Vaccines" section describes vaccines comprising "the polysaccharide-protein conjugates which generate antibodies that are reactive against the polysaccharide or oligosaccharide and hence reactive against the organism or cell from which the polysaccharide or oligosaccharide was isolated." The "Antibodies" section describes producing antibodies directed against the polysaccharide-protein conjugate by administering immunogenic β-propionamido-linked polysaccharide-protein conjugate into a host animal. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

(f) Claim 16 stands rejected to for the limitation "conjugate that elicits protective antibodies" as being unclear as to what the antibodies are protective against. In order to address the Examiner's concerns, applicants have amended claim 1 to read - -elicits protective antibodies reactive against the polysaccharide or oligosaccharide- -. Support is provided in the instant specification under sections "C. Vaccines" (pg. 12, lns. 1-6) and "E. Antibodies" (pg. 14, lns. 23-27). The "Vaccines" section describes vaccines comprising "the polysaccharide-protein conjugates which generate antibodies that are reactive against the polysaccharide or oligosaccharide and hence reactive against the organism or cell from which the polysaccharide or oligosaccharide was isolated." The "Antibodies" section describes producing antibodies directed against the polysaccharide-protein conjugate by administering immunogenic β-propionamido-linked polysaccharide-protein conjugate into a host animal. Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(g) Claim 16 stands rejected for being vague and indefinite in the recitation "antibodies produced by a method comprising: A) B) C)." As suggested by the Examiner, applicants have replaced the recitation "antibodies produced by" with - - antibodies, wherein said conjugate is produced by - - in order to address the Examiner's concerns. Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

(h) Claims 2-5, 8-15, 17-28, 37-40, and 59-63, which depend directly or indirectly

from claim 1 or claim 16, stand rejected under 35 U.S.C. §112, second paragraph as being indefinite and vague because they depend from a rejected base claim(s). As the base claims have been amended to address the Examiner's concerns, applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

35 U.S.C. §103

36) Claims 1 and 8-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Pon, RA (The Study of Polysialic Acid Conjugates, Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) in view of Blake, et al. (U.S. 5,439,808). Applicants respectfully traverse the Examiner's grounds for rejection because to establish *prima facie* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 180 USPQ 580 (CCPA 1974).

Pon in view of Blake does not teach or suggest all of the claim elements recited by claim 1. For instance, the percent of polysaccharide or oligosaccharide that is de-N-acetylated varies from the present invention to what is reported in the Pon reference. Pon reports the conjugation of N-acryloyl colominic acid to BSA or IgG, wherein the colominic acid has only been de-N-acetylated by about 15%. For example, at page 181, Pon cites: "BSA (4-17) (5 mg) or IgG (4-36) (5 mg) was combined with 15% N-acryloylated colominic acid (4-16) (10 mg) and dissolved in 200 µl borate buffer (0.1M; pH 8.3)." The other Pon conjugates produced by Michael-type addition (the N-acryloyl derivative conjugates) also do not possess all of the claim limitations. Specifically, these derivative conjugates are not re-acryloylated at de-N-acetylated termini. Pon also does not teach or suggest that 15% N-Acryloylated colominic acid conjugates can elicit the production of protective antibodies. Because the sugar is only 15% acryloylated, the degree of protein coupling is limited and will therefore negatively impact the effectiveness of an immune response.

In contrast, the polysaccharide or oligosaccharide of the instant invention has at least 50% of the N-acetyl groups removed as described in the instant specification (pg. 6, lns. 10-17) and amended in claims 1 and 16. Accordingly, the Pon publication does not render obvious the instant invention. Furthermore, conjugates of the instant application are also highly acryloylated and have been shown to produce productive immune responses. The specification states the degree of acryloylation of the claimed N-propionated saccharides:

"The resulting N-acryloylated polysaccharide or N-acryloylated oligosaccharide is at least about 95% acryloylated or greater." (page 9, first paragraph). The instant specification discloses the immunogenicity of β-propionamido-linked polysaccharide-protein conjugates in Tables 5-8 (pages 24-27) as observed by ELISA and opsonophagocytic assays. Therefore, since the Pon conjugates are only de-acetylated by about 15% and have such a lower percent acryloylation, the conjugates would not be expected to produce a protective immune response.

Blake, et al. report a porin protein-polysaccharide conjugate and method of preparing the conjugate, where the polysaccharide is from a *Neisseria meningitidis* organism. Blake further relates to the use of porin as a protein carrier in conjugate vaccines, but does not teach or suggest the conjugate vaccines of the present invention which possess the β-propionamido linkage. However, this reference is silent regarding the claimed element where at least 50% of the N-propionated polysaccharide is de-N-acetylated. Blake, et al. does not report a protein-polysaccharide conjugate where the polysaccharide is de-N-acetylated. Analysis of the conjugate shows 43% polysaccharide by weight. However, there is no mention of the percentage of de-N-acetylated polysaccharides.

Therefore, as the primary publication of the Examiner's combination fails to provide motivation for one to make a conjugate according to the claimed invention, these 103(a) rejections are improper. Further, if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). In view of applicants' amended claims where the recitation "at least 50% of the N-propionated polysaccharide or N-propionated oligosaccharide is de-acetylated" is added, the Pon and Blake references in combination, do not teach or suggest the claimed invention. Applicants respectfully request reconsideration and withdrawal of this §103(a) rejection.

37) Claims 1, 16, and 22-24 stand rejected under 35 U.S.C. §103(a) over Pon, RA in view of Blake, et al. Applicants respectfully disagree with this rejection.

The Examiner readily admits that Pon does not teach or suggest a conjugate composition further comprising an adjuvant. The Examiner further refers to Blake, et al. as reporting a meningococcal group B porin protein, fusion protein, or conjugate vaccine having

adjuvants which enhance the production of porin-specific antibodies. However, as previously discussed, Pon or Blake, et al. do not teach or suggest the conjugate composition as claimed in the present invention. Furthermore, the combination of the conjugate vaccine comprising adjuvants of Blake, et al. and the conjugate composition of the Pon reference does not provide any guidance for one skilled in the art to prepare a polysaccharide-protein conjugate, where at least 50% of the polysaccharides are de-N-acetylated. Therefore, applicants respectfully request reconsideration and withdrawal of this §103 rejection.

40) Claims 1-4, 11-14, 16, 17, 19-22, 26-28, 37-39, and 59-63 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Pon, RA and Blake, et al. (U.S. 5,439,808). Applicants respectfully disagree with the Examiner's grounds for rejection.

The Examiner contends that varying the percentages of N-acryloylation or de-N-acetylation of the polysaccharide or oligosaccharide is within the realm of routine experimentation for optimization purposes and that there is no evidence establishing that the recited percentages are critical for the invention. However, applicants point out that Pon in combination with Blake, does not provide any motivation to adjust the percentage of acetyl groups that are removed. In fact, applicants respectfully direct the Examiner's attention to pages 202 of the Pon publication, where Pon reports that "it was quite evident that antigenicity of the polysaccharide was lost after 55% of the polysaccharide was de-N-acetylated." Table 5-2 however, shows that colominic acid having 45.6% de-N-acetylation loses antigenicity of the polysaccharide; and, beyond 57.7%, antigenicity is eliminated. Therefore, Pon provides no motivation for one skilled in the art to modify the percentage of de-N-acetylation of the polysaccharide beyond 15% as reported. There is no motivation for the skilled artisan to combine the Pon and Blake references in order to obtain a polysaccharide-protein conjugate of the claimed invention. In fact, neither of these references teach or suggest a polysaccharide-protein conjugate where at least 50% of the acetyl groups of the polysaccharide are removed and the polysaccharide may still elicit protective antibodies. Reconsideration and withdrawal of this §103(a) rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. , Order No. 3842-4043US1.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 3842-4043US1. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

By: _____
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Dated: February 28, 2003

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VERSION OF THE AMENDMENTS TO THE CLAIMS AND SPECIFICATION SHOWING DELETIONS AND ADDITIONS

IN THE CLAIMS:

1. (Twice Amended) A polysaccharide-protein conjugate or oligosaccharide-protein conjugate comprising an N-propionated polysaccharide or N-propionated oligosaccharide directly coupled to a protein at a β-position of a propionate moiety; wherein the N-propionated polysaccharide or N-propionated oligosaccharide directly coupled to the protein at the β-position of the propionate moiety elicits protective antibodies reactive against the N-propionated polysaccharide or N-propionated oligosaccharide; wherein the N-propionated polysaccharide or N-propionated oligosaccharide is de-N-acetylated and N-acryloylated at the de-N-acetylated terminus; wherein at least 50% of the N-propionated polysaccharide or oligosaccharide is de-N-acetylated; and wherein the protein is a bacterial protein or a synthetic protein containing lysine or cysteine residues.

4. (Third amendment) The conjugate[conjugates] according to claim 1 wherein the [the] polysaccharide or oligosaccharide is [derived from a polysaccharide] obtained from *Escherichia coli*, Meningococcus, Pneumococcus, Streptococcus, Neisseria, Salmonella, Klebsiella, or Pseudomonas.

15. (Third amendment) The conjugate[conjugates] according to claim 1 wherein the polysaccharide or oligosaccharide is [derived from a polysaccharide] obtained from group B *Streptococcus* type III, and wherein the protein is tetanus toxoid.

16. (Third amendment) A polysaccharide-protein conjugate or oligosaccharide-protein conjugate that elicits protective antibodies reactive against the polysaccharide or oligosaccharide, wherein said conjugate is produced by a method comprising:

A) de-N-acetylating an isolated polysaccharide or oligosaccharide using a de-N-acetylating reagent to form a de-N-acetylated polysaccharide or a de-N-acetylated oligosaccharide, wherein the isolated polysaccharide or oligosaccharide is at least 50% de-N-acetylated;

B) N-acryloylating the de-N-acetylated polysaccharide or the de-N-acetylated oligosaccharide at a de-N-acetylated terminus with an acryloylating reagent to form an N-propionated polysaccharide or an N-propionated oligosaccharide, and

C) directly coupling at a β-position of a propionate moiety of the N-propionated polysaccharide or the N-propionated oligosaccharide to a protein to form the polysaccharide-protein conjugate or the oligosaccharide-protein conjugate; wherein the protein is a bacterial protein or a synthetic protein containing lysine or cysteine residues.

59. (Amended) The conjugate[conjugates] according to claim 1, wherein the de-N-acetylated polysaccharide[s are] or de-N-acetylated oligosaccharide is at least 95% N-acryloylated.

60. (Amended) The conjugate[conjugates] according to claim 16, wherein the de-N-acetylated polysaccharide or the de-N-acetylated oligosaccharide is at least 95% N-acryloylated.

61. (Amended) The conjugate[conjugates] according to claim 1, wherein the N-propionated polysaccharide[s are] or N-propionated oligosaccharide at least 50% de-N-acetylated.

62. (Amended) The conjugate[conjugates] according to claim 16, wherein the de-N-acetylated polysaccharide or the de-N-acetylated oligosaccharide is at least 50% de-N-acetylated.

63. (Amended) The conjugate[conjugates] according to any one of claim 1 and claim 16, wherein the bacterial protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, cholera toxin subunit B, *Neisseria meningitidis* outer membrane proteins, pneumolysoid, C-β protein from group B Streptococcus, *Pseudomonas aeruginosa* toxoid, and pertussis toxoid.

IN THE SPECIFICATION

Please replace the first sentence of the instant specification with the following:

This [is a continuation-in-part of co-pending] application claims priority under 35 U.S.C. §119(e) for Provisional Application [application] Serial No. 60/097,120, filed August 19, 1998, by Michon, et al. and entitled, "Immunogenic Polysaccharide-Protein Conjugate Useful As A Vaccine Produced Via Conjugation Through A C2-3 N-Acyl Portion Of A Polysaccharide."